DICLOFOP-METHYL

PC Code: 110902

Evaluation of Toxicology Database for the Reregistration Eligibility Document Disciplinary Chapter

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1.0 HAZARD CHARACTERIZATION

Diclofop-methyl [2-(4-(2',4'-dichlorophenoxy)phenoxy)propionic acid, methyl ester] is the active ingredient of Hoelon, which is currently registered as a herbicide for use on food crops (wheat, barley) and golf course turf. Hoelon 3EC is the only registered end-use product.

Toxicological database for diclofop-methyl was reviewed for determination of hazard identification and selection of hazard endpoints for risk assessment. Acute, subchronic and chronic toxicity studies, as well as developmental, reproductive toxicity, and metabolism studies, were available, complete, and acceptable. The required carcinogenicity and mutagenicity studies were also reviewed and found to be acceptable. Since no neurotoxicity was observed in any of the core studies, therefore, the acute and subchronic neurotoxicity studies in the rat are not required. No special toxicology studies were submitted.

Diclofop-methyl is moderately toxic by oral or dermal exposure (toxicity category II), but less so by inhalation (toxicity category IV). In the primary irritation studies, diclofop-methyl produced slight ocular irritation (toxicity category III) and slight dermal irritation (toxicity category IV).

The toxicity of diclofop-methyl was evaluated in subchronic feeding studies in the mouse and rat, a 21-day dermal toxicity study in the rat, and chronic feeding studies, two in the rat and one in the dog. In the subchronic and chronic feeding studies, serum activities of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) were all increased; in the dermal toxicity study only ALP activity was increased. The elevated enzyme activities are indicative of hepatotoxicity. Evaluations at terminal sacrifice revealed treatment-related effects, primarily in the liver. These effects included increased liver weights and increased incidence of non-neoplastic histopathological lesions. In the subchronic studies, centrilobular hepatocellular hypertrophy was observed in both rats and mice, by both routes of administration. In the chronic studies, centrilobular hypertrophy and other liver lesions (e.g. lipofuscin storage, eosinophphilic and basophilic foci, and necrosis) were observed in one of the rat studies, while in the other study, foam cell aggregation was observed in the lungs of male rats. In the chronic dog study, females showed fatty changes in the liver.

The acceptable carcinogenicity studies in the rat and mouse showed increased incidence of neoplastic lesions. A second carcinogenicity study in the rat was reviewed, but it was determined that the maximum tolerated dose was not achieved. Hepatocellular adenomas and carcinomas were significantly increased in male and female rats. Leydig cell tumors and adrenal medullary adenomas were observed in males, while uterine polyps and thyroid follicular cell adenomas were observed in females. In the mouse carcinogenicity study, the liver was again identified as a target organ (increased AP, increased liver weights, hepatocellular hypertrophy).
Significant increases in hepatocellular adenomas and carcinomas were observed in both male and female mice. Even though diclofop-methyl is carcinogenic in rats and mice, the mutagenicity studies with were all negative.

Based on increased incidence of neoplastic lesion observed in the mouse carcinogenicity study, the Cancer Assessment Review Committee (CARC) classified diclofop-methyl as a likely

human carcinogen with a Q_1* of 2.3 x 10^{-1} (mg/kg/day)$^{-1}$.

Diclofop-methyl was also evaluated for developmental and reproductive toxicity; no increased susceptibility of fetuses/pups was observed. No developmental toxicity was observed in rats at doses of diclofop-methyl which produced maternal toxicity (increased liver weights); developmental effects (decreased fetal body weight and crown-rump length) were seen only at maternally toxic doses. No developmental toxicity was observed in the rabbit study; at the highest dose tested does showed hepatic toxicity (increased liver weights) and decreased body weight gains. In a two-generation (one litter) reproduction study in the rat, treatment-related effects were observed across generations in both sexes; in some cases pups were affected. Systemic toxicity in adult rats included increased liver weights and histopathological lesions in the liver and kidney, pup liver weights were also increased. Reproductive toxicity (reduced fetal body weights and delayed physical development) were observed at doses higher than those which produced systemic toxicity in adult animals.

Peroxisome proliferation, measured either indirectly or directly, was observed in both rats and mice; but not dogs. Although detailed mechanistic studies have not been carried out with diclofop-methyl, the subchronic toxicity studies in the rat and mouse included measurement of enzyme activities (catalase, malic enzyme) used as indirect markers for peroxisome proliferation. In both of these studies, activities of enzymes were significantly increased. In the rat feeding study, histopathological findings (cytoplasmic granulation in the liver) was also suggestive of peroxisome proliferation; electronmicrographs (high-dose group only, one rat/sex) showed an increase in peroxisomes associated with an increase in smooth endoplasmic reticulum.

A policy regarding the role of peroxisome proliferation in hepatic carcinogenicity has not been formally addressed by the Agency, however, there is growing evidence that the observed nongenotoxic hepatocarcinogenicity in rodents is a result of peroxisome proliferation. Other pesticides in the same chemical class (clodinafop-propargyl, lactofen, haloxyfop-methyl, fluazifop-butyl, clofop-isobutyl, oxyfluorfen, fomesafen sodium, acifluorfen sodium, nitrofen, quizalofop-ethyl) as diclofop-methyl produce peroxisome proliferation and are carcinogenic.

The Mechanism of Toxicity Assessment Review Committee (MTARC) reviewed the data for diclofop-methyl using the criteria established by an ILSI workshop on peroxisome proliferation and human risk assessment [Cattley et al. Regul Toxicol. Pharmacol. 27: 47-60 (1998)]. The MTARC concluded that, while the data is highly suggestive of diclofop-methyl as being a peroxisome proliferator, the submitted studies lack the depth and quality to unequivocally establish peroxisome proliferation as the mechanism of action for non-genotoxic hepatocarcinogenicity of diclofop-methyl.

2.0 TOXICITY DATA REQUIREMENTS

The requirements (CFR 158.135) for diclofop-methyl are in Table 1.

Table 1. Toxicity Studies Data Requirements with Diclofop-methyl, Technical

Guideline		Required	Satisfied
870.1100	Acute Oral Toxicity	Y	Y
870.1200	Acute Dermal Toxicity	Y	Y
870.1300	Acute Inhalation Toxicity	Y	Y
870.2400	Primary Eye Irritation	Y	Y
870.2500	Primary Dermal Irritation	Y	Y
870.2600	Dermal Sensitization	Y	Y
870.6100	Acute Delayed Neurotoxicity (Hen)	N	--
870.6200	Acute Neurotoxicity Screening Battery (Rat)	N	--
870.3100	Oral Subchronic (Rodent)	Y	Y
870.3150	Oral Subchronic (Non-Rodent)	Y	Y
870.3200	21-Day Dermal	Y	Y
870.3250	90-Day Dermal	N	--
870.3465	90-Day Inhalation	N	--
870.6100	90-Day Neurotoxicity (hen)	N	--
870.6200	90 Day Neurotoxicity Screening Battery (Rat)	N	--
870.4100a	Chronic Toxicity (Rodent)	Y	Y
870.4100b	Chronic Toxicity (Non-rodent)	Y	Y
870.4200a	Oncogenicity (Rat)	Y	Y
870.4200b	Oncogenicity (Mouse)	Y	Y
870.3700a	Developmental Toxicity (rodent)	Y	Y
870.3700b	Developmental Toxicity(non-rodent)	Y	Y
870.3800	Reproduction	Y	Y
870.4300	Chronic/Oncogenicity	Y	Y
870.6300	Developmental Neurotoxicity	N	---
870.5100	Mutagenicity—Gene Mutation	Y	Y
870.5385	Mutagenicity—Structural Chromosomal Aberrations	Y	Y
870.5550	Mutagenicity—Other Genotoxic Effects	Y	Y
870.7485	General Metabolism	Y	Y
870.7600	Dermal Penetration	Y	Y
870.7200	Domestic Animal Safety	N	--
Special Studies for Ocular Effects		N	--
	Acute Oral (Rat)	N	--
	Subchronic Oral (Rat)	N	--
	Six-month Oral (Dog)	N	--

Y - Yes; **N** - No

3.0 DATA GAP(S)

The database for diclofop-methyl is complete, there are no data gaps.

4.0 HAZARD ASSESSMENT

4.1 Acute Toxicity

Adequacy of data base for acute toxicity: The data base for acute toxicity is considered complete. No additional studies are required at this time.

The acute toxicity data on the diclofop-methyl, technical is summarized below in Table 2.

Table 2. Acute Toxicity Data on Diclofop-methyl

OPPTS Guideline No.	Study Type	MRID Nos	Results	Toxicity Category
870.1100	Acute Oral	41476001 92036052	Male: 481 mg/kg Female: 500-630 (estimate) mg/kg Combined 512 (428-636) mg/kg	II
		00123982	Male: 580 mg/kg	II
		00123983	Female: 557 mg/kg	II
870.1200	Acute Dermal	00071522 92036013	Male: 580 mg/kg	II
		00032595	Female: 557 mg/kg	II
870.1300	Acute Inhalation	00032595	Male and female > 3.83 mg/L	IV
		41573304	Male and female > 4.75 mg/L	IV
		00032595	Male and female > 3.83 mg/L	IV
870.2400	Primary Eye Irritation	42428601	Slight ocular irritant, Conjunctival redness and discharge at 24 hr, cleared by 72hr	III
870.2500	Primary Skin Irritation	40213506	Slight irritant, PII = 0.8 (0 to 72 hr)	IV
870.2600	Dermal Sensitization	41476003 92036047	Buehler: Negative	NA
		41476002 41476003 92036046	Maximization: Moderate to severe sensitizer	NA

4.2 Subchronic Toxicity

Adequacy of data base for subchronic toxicity: The data base for subchronic toxicity is considered complete. No additional studies are required at this time.

Subchronic feeding studies in the rat and mouse and dermal toxicity study in the rat identified the liver as the primary target organ for toxicity. Liver weights were increased in treated animals in all of these studies; histological examination revealed an increased incidence hepatic lesions. Enzyme markers (malic enzyme, catalase), used as indirect biomarkers for peroxisome proliferation, were increased in both of the oral studies, and in general, returned to control levels after a treatment-free recovery period.

4.2.1 OPPTS 870.3100 Subchronic Oral Toxicity Feeding - Rat

Executive Summary: In this subchronic toxicity study (42573301), Wistar rats (20/sex/dose) were fed diets containing diclofop-methyl at concentrations of 0 (basal diet), 5, 20, 80, or 320 ppm (0, 0.34, 1.6, 6.3, or 26 mg/kg/day, males; 0, 0.44, 1.8, 7.1, 28 mg/kg/day, females) for 13 weeks, followed by a four-week, treatment-free (basal diet) recovery period with 10 rats/sex in the control, 80, and 320 ppm groups.

No treatment-related clinical signs or deaths occurred during the study. Males dosed at 320 ppm, had significantly ($p \leq 0.05$) decreased mean body weights (9-11%) and body weight gains (12 to 14%) at 46 and 92 days of treatment; body weights were decreased (8.4%, not significant) at 120 days. At the end of the recovery period, the body weights of high-dose males were still reduced (9%, not significant). The body weights of females were unaffected by treatment. Food consumption by high-dose males were decreased 4 to 14% (not significant) during the study. For the remaining treatment groups, food and water consumption were comparable to the control groups of both sexes.

Clinical pathology revealed treatment-related changes in some hematological and clinical chemistry parameters. Coagulation times and thromboplastin times were significantly decreased (19% and 31%, respectively) in high-dose males, but returned to control levels at the end of the recovery period. Clinical chemistry effects in 80 and 320 ppm males included decreases in cholesterol (29 and 45%, respectively) and total lipids (26 and 42%, respectively); free fatty acids were decreased in 80 ppm females (28%) and high-dose males (55%) and females (19%). In males, AST (SGOT) and ALT (SGPT) were increased at 320 ppm (20 and 30%, respectively); ALP was increased at 80 and 320 ppm in males (38 and 61%, respectively) and females (42 and 46%, respectively). At the end of the recovery period, only free fatty acid levels were still decreased at 80 and 320 ppm in males (26 and 23%, respectively) and females (24 and 20%, respectively).

Selected liver enzymes, used as indirect biomarkers for peroxisome proliferation and microsomal enzyme induction were measured at the ends of the main study and recovery period. Assay of liver homogenates showed increases in malic enzyme and catalase, both indirect enzyme markers for peroxisomal proliferation. Malic enzyme was significantly increased in 80 ppm and 320 ppm males (65 and 96%, respectively) and 320 ppm females (42%). Catalase was significantly increased in 5, 20, and 80 ppm females (85 to 189%) and in 320 ppm males (146%) and females (474%). Microsomal enzymes (glycerophosphate dehydrogenase, $NADPH_2$-dependent cytochrome c reductase and glucuronyltransferase) were induced in 80 ppm females and/or 320 ppm males and females; ethylresorufin o-deethylase activity was decreased in 80 ppm males and 320 ppm males and females. At the end of the recovery period, there was no increase in enzyme activity associated with peroxisome proliferation; glucuronyltransferase activity was still increased in 80 and 320 ppm males

and females.

Treatment-related pathological changes were limited to the liver. Absolute and relative liver weights were significantly increased in 80 and 320 ppm males and absolute liver weights, in 320 ppm females. Histopathological evaluations revealed centrilobular lesions with marked cytoplasmic granulation (suggestive of peroxisome proliferation). Electronmicrographs of the high-dose animals (1/sex) showed an increase in peroxisomes associated with an increase in smooth endoplasmic reticulum.

The LOAEL was established at 80 ppm (6.3 mg/kg/day, males; 7.1 mg/kg/day, females) was based clinical chemistry effects (increased ALT, AST, ALP, malic enzyme and catalase and decreased cholesterol and free fatty acids) and centrilobular hypertrophy in the liver. The NOAEL was established at 20 ppm (1.6 mg/kg/day, males; 1.8 mg/kg/day, females).

The study is acceptable (guideline) and fulfills the requirement for subchronic toxicity study (82-1, 870.3100) the rat.

4.2.2 OPPTS 870.3100 Subchronic Oral Toxicity Feeding - Mouse

Executive Summary: In a subchronic toxicity study (MRID 42593901) diclofop-methyl was administered to 10 - 15 NMRI mice/sex/dose at the dose levels of 0, 2, 6.3, 20, and 63 ppm (0, 0.3, 1.0, 3.3, 10.4 mg/kg/day, males; 0, 0.4, 1.2, 3.8, 12.4 mg/kg/day, females) for 13 weeks. At the end of treatment, 5 mice/sex, in the control, 20, and 63 ppm doses groups, were carried over to a 4-week, treatment-free (basal diet) recovery phase.

There were no treatment-related clinical signs or deaths during the study. Males dosed at 63 ppm, had significantly decreased mean body weights (8-11%) and body weight gains (16 to 18%) after 44 and 92 weeks of treatment; at the end of the recovery period, the body weights of control and high-dose males were comparable. The body weights of females were unaffected by treatment. Feed consumption was comparable between treated and control groups.

Treatment-related changes in some hematological and clinical chemistry parameters, as well as changes in activities of selected enzymes in liver homogenates, were observed. Coagulation times in high-dose males were significantly decreased (29%) after 13-weeks of treatment, but returned to control values after the recovery period. In males, triglyceride and total lipids were increased at 6.3 ppm and higher doses; AST, ALT, and ALP were increased at 20 ppm and higher. For females, cholesterol and ALP activities were increased at 20 ppm and higher, while increases in triglycerides and ALT (SGPT) were observed only at the high-dose. At the end of the recovery period, clinical chemistry parameters, except for ALT activities in females, returned to control values.

Assay of liver homogenates showed increases in malic enzyme and catalase, both indirect enzyme biomarkers for peroxisomal proliferation. Malic enzyme was increased in all treated male groups (101 to 785%) and females dosed at 6.3 ppm and higher(50 to 350%); catalase was increased in 6.3 ppm males (484%) and 20 and 63 ppm males (785 and 367%, respectively) and females (446 and 357%, respectively). At the end of the recovery period, catalase (males and females) and malic enzyme (females only) returned to control values. Microsomal enzymes ($NADPH_2$-dependent cytochrome c reductase and/or glycerophosphate dehydrogenase) were induced in all treated males

and or females. At the end of the recovery period, increased activity was still observed at the high-dose level in both sexes.

Treatment-related pathological changes were limited to the liver. Absolute and relative liver weights were significantly increased in a dose-dependent manner at 6.3 ppm and higher. Dose-related increases in single cell necrosis were observed in both sexes at 2 ppm and higher. Kupffer cell proliferation, enlargement of centilobular hepatocytes with loss of basophillia (an indication of microsomal enzyme induction), and liver cell mitosis were observed in males dosed at 6.3 ppm and higher and females dosed at 20 ppm and higher. These three hepatic lesions were observed in essentially all of the high-dose animals. Increased liver cell mitosis was observed in males dosed at 6.3 ppm and females dosed at 63 ppm.

The LOAEL was established at 2 ppm (0.3 mg/kg/day, males; 0.4 mg/kg/day, females) was based upon hepatotoxicity including increases in peroxisomal proliferation, microsomal enzyme induction, and liver necrosis. The NOAEL was not established.

The study is acceptable (guideline) and fulfills the requirement for subchronic toxicity study (82.1, 870.3100) the mouse.

4.2.3 OPPTS 870.3200 Repeated Dose Dermal – Rat

Executive Summary: In a repeated-dose dermal toxicity study (MRID 41476004), diclofop-methyl (Hoe 023408 OH ZD95 0003 Technical; 94.5% a.i.) was applied to the clipped intact skin of 11 Wistar rats/sex/dose at nominal dose levels of 0 (diluent-treated control), 5, or 125 mg/kg/day (<limit dose), and to the clipped intact skin of six Wistar rats/sex/dose at a nominal dose level of 25 mg/kg/day for 6 hours/day, 5 days/week, for a total of 21 applications during a 30-day period. Five rats/sex in the control, 25, and 125 mg/kg/day groups were maintained for a 4-week recovery period to determine the reversibility of effects.

All animals survived the 30-day study. No treatment-related signs of dermal toxicity were observed. No treatment-related differences in toxicity, body weights, food consumption, urinalysis, or gross pathology were observed between the control and treated groups, and no neoplastic tissue was observed. Signs of systemic toxicity were observed in the livers of the 25 and 125 mg/kg/day animals.

At 25 mg/kg/day, absolute and relative liver weights were increased (males, each ↑35%; females, ↑20-21%; $p \leq 0.05$) when compared to concurrent controls. Males displayed dose-dependent increases ($p \leq 0.05$) in mean ALP activity (↑32%) and $gamma_1$-globulins (↑8%) and females displayed a dose-dependent increase in $alpha_1$-globulin levels (↑21%; $p \leq 0.05$).

At 125 mg/kg/day, the liver and lipid metabolism were adversely affected. Enlarged (not tested for statistical significance) centrilobular hepatocytes were observed in 5/11 males and 3/11 females vs 0/22 controls (mean enlargement, 20.3% in males; 45.4% in females) and remained enlarged (↑20%) in females at the end of the recovery period. Absolute and relative liver weights were increased ($p \leq 0.05$) in males (↑53% and ↑60%, respectively) and females (↑57% and ↑48%, respectively) at the end of the treatment period and remained higher in the females (↑14-17%;

$p \leq 0.05$) following the recovery period. Males displayed ($p \leq 0.05$) increased mean ALP activity (↑42%) and decreased cholesterol levels (30%) and females exhibited ($p \leq 0.05$) a prolonged activated partial thromboplastin time (↑299%) and increased levels of triglycerides (↑43%), total protein (↑12%), and $alpha_1$-globulin (↑22%).

The systemic LOAEL is 25 mg/kg/day, based on increased liver enzymes, proteins, and absolute and relative liver weights. The systemic NOAEL is 5 mg/kg/day. The dermal LOAEL was not observed. The dermal NOAEL was ≥125 mg/kg/day.

This study is classified acceptable (guideline) and satisfies the guideline requirement (§82-2) for a repeated-dose dermal toxicity study.

4.3 Prenatal Developmental Toxicity

Adequacy of data base for Developmental Toxicity: The data base for developmental toxicity is considered complete. No additional studies are required at this time.

Developmental toxicity studies were carried out in the rat and rabbit. In the rat study, developmental toxicity was observed only at maternally toxic doses. Systemic maternal toxicity was observed at the lowest dose tested and consisted of increased absolute and relative liver weights. At the mid-dose level, decreased fetal body weight and decreased crown-rump length, distended ureters, and skeletal abnormalities were observed. In the rabbit study no developmental toxicity was seen; maternal toxicity, consisting of increased liver and kidney weights, decreased body weights, and reduced food consumption, was observed only at the high-dose.

4.3.1 OPPTS 870.3700a Prenatal Developmental Study - Rat

Executive Summary: In a developmental toxicity study (92036042), pregnant Wistar rats (20 to 25/dose) were dosed with diclofop-methyl (96%) at 0 (vehicle, sesame oil), 10, 32, or 100 mg/kg/day from gestation day (GD) 6 through 15.

Twelve of the 20 high-dose animals died between days 13 and 21 of pregnancy. Prior to death these animals were emaciated, had blood crusts on the nasal orifice, and were hypoactive. Remaining high-dose animals and those of the other treatment groups were not impaired. At terminal sacrifice, body weight of surviving high-dose dams was 20% lower than the control value; statistically, but not biologically (5%), significant decreases in body weight were noted in the mid-dose group. At the low-, mid- and high-dose levels, absolute liver weights were significantly increased (all greater than the historical control range) by 11.6%, 9.8%, and 23.1%, respectively, and relative liver weights, by 13%, 15%, and 48%, respectively. Because the liver is a target organ of toxicity, the effects on liver weights at the low-dose were considered treatment-related.

Due to the high mortality in the high-dose group, only 19 viable fetuses were available at terminal sacrifice. The number of live fetuses of the remaining low- (240) and mid- (194) were comparable to the control value (218). Fetal body weights were significantly decreased by 12.5% and 34% at the mid- and high-dose levels, respectively, and crown/rump lengths by 5.8% and 18% at the mid- and high-dose levels, respectively.

With the exception of the intercurrent deaths in the high-dose group, all gestation and caesarean section parameters of treated animals were all comparable to controls. Visceral and skeletal abnormalities were evaluated by necropsy and body cross section examinations. At necropsy, visceral abnormalities consisted of increased percentages of enlarged and blood-filled heart [60% (33%)] at the high-dose level. Body cross section examination included the above abnormalities and the addition of increased percentage of distended ureter in the mid- [7.6% (28%)] and high- [22 % (33%)] dose groups. Skeletal abnormalities for fetuses (litters) at the mid- and high-dose groups included fragmented thoracic centra [5.9% (27%) and 50% (100%), respectively], weakly/non-ossified sternebrae [69% (94%) and 100% (100%), respectively] and non-ossified 5th metacarpal [62% (94%) and 100% (100%), respectively]. Although the incidence of non-ossified 5th metacarpal was increased in the low-dose group, the value was within the historical control range. At the high-dose slight/non-ossified skull bones [100% (100%)], weakly/non-ossified sacral vertebrae [40% (67%)] and pelvic girdle [20% (67%)], and non-ossified 1st - 5th toes [60% (100%)] were also observed.

Based on the results of the study (increased absolute and relative liver weights), the LOAEL for maternal systemic toxicity was established at 10 mg/kg/day, the NOAEL was not established.

Based on the results of this study (significant decreases in fetal body weight and crown-rump length, distended ureters, and skeletal abnormalities), the LOAEL for developmental toxicity was established at 32 mg/kg/day, the NOAEL was established at 10 mg/kg/day.

This study is acceptable-guideline, and satisfies requirements [870.3700, §83-3(a)] for a developmental toxicity study in the rat.

4.3.2 OPPTS 870.3700b Prenatal Developmental Study - Rabbit

Executive Summary: In a developmental toxicity study (MRID 92036043), diclofop- methyl (Hoe 23408, 97±2.0% a.i.) in sesame oil was administered by gavage to pregnant Himalayan rabbits at concentrations of 0, 0.03, 0.3, or 3.0 mg/kg/day on gestation days (GDs) 7 through 19. Does were sacrificed on GD 29.

Two does each from the 0.03 and 3.0 mg/kg groups and one doe from the 0.30 mg/kg group delivered prematurely from GDs 25-29. No premature deaths occurred and no treatment-related clinical signs were observed.

When compared to concurrent controls, no treatment-related changes were observed in body weights at any dose level. During treatment, non-statistically significant (NS) decreases in body weight gains were observed in high-dose does during GDs 7-14 (14.6 g vs 35.3 g, control) and GDs 14-20 (-60 g vs -8.3 g control). During the post-treatment period (GDs 20-29), body weight gains were increased (NS) in high-dose does (217 g) compared to controls (115 g). Overall (GDs 0 - 29), body weight gains for high-dose does were slightly increased (NS) in high-dose does (177 g) compared to controls (126 g). During the treatment period (GDs 7 - 20), decreases of 5 to 35% (NS) in relative (g/kg/day) food consumption in high-dose does; during the post-treatment period decreases (NS) of 10% were still observed.

At necropsy, significant increases ($p<0.05$) were observed in absolute liver (15%) and kidney weights (29%) when compared to concurrent controls. Cesarean section data did not show any changes in the number of implantations/doe, resorptions/doe, postimplantation losses, and percent male were similar between control and treated groups. No treatment-related changes were observed upon macroscopic examination of the does.

External, skeletal, and visceral fetal examinations did not reveal any treatment-related effects.

The maternal LOAEL is 3.0 mg/kg/day, based on significantly increased absolute liver and kidney weights, decreased body weight gain, and reduced food consumption.

The maternal NOAEL is 0.30 mg/kg/day.

No treatment-related developmental effects were noted at any dose level.

The developmental LOAEL was not established.
The developmental NOAEL is $\geq$ 3.0 mg/kg/day.

This developmental toxicity study is classified acceptable (guideline) and satisfies the guideline requirements [§83-3(b)] for a developmental toxicity study in the rabbit.

4.4 Reproductive Toxicity

Adequacy of data base for Reproductive Toxicity: The data base for reproductive toxicity is considered complete. No additional studies are required at this time.

4.4.1 OPPTS 870.3800 Two-Generation Reproduction Study - Rat

Executive Summary: In this two-generation (one-litter/generation) reproduction study (42060501, 42560501) male and female rats [Crl:CD(SD)BR Sprague-Dawley] were continuously dosed with diclofop-methyl at dietary concentrations of 0, 10, 30, or 100 ppm (males: 0, 0.7, 2.1, 7.3 mg/kg/day; females: 0, 0.9, 2.5, 8.4 mg/kg/day) for two consecutive generations.

No treatment-related clinical signs or mortalities were observed. Significant changes in body weights, body weight gains, and food consumption were noted, the differences were considered to be incidental and not related to treatment.

Changes in organ weights were observed in mid- and high-dose males and females. Liver weights were increased across generations (adults and pups) in both males and females. F0 and F1 adults showed increased absolute and relative (males only) liver weights at the high-dose level; mid-dose F0 females also had increased absolute and relative liver weights. Liver weights of F1 pups were not affected by treatment, however, the absolute liver weights were increased in mid- and high-dose F2 pups. Kidney weights were increased in mid- and high-dose F1 adult males and high-dose F0 adults. Kidney weights were decreased in F1 (males only) and F2 pups at the high-dose level. F1 and F2 pups also had decreased spleen, adrenal and uterus weights; in F2 males, testes weights were also decreased.

Treatment-related histopathological effects were observed at the high-dose level in the liver, and, to a lesser degree, in the kidneys of both sexes and generations. Liver lesions (loss of intracytoplasmic irregular empty space and cellular hypertrophy and functional swelling of the nucleus of hepatocytes) were observed in a high percentage (> 68%) of F0 and F1 adults and F2 pups; increased incidence of foci of altered clear cells was observed in F1 adults (28 - 56%). The kidneys of high-dose animals showed yellow-brown intracytoplasmic pigment deposits in the convoluted tubule in F0 adults (44 - 56%), focal subacute to chronic interstitial nephritis in F1 adult males (52%), hyaline casts in F1 adults (24 - 72%) and calcified deposits in the medulla in F1 pups (> 48%).

At the high-dose level, effects included significant delays in developmental growth. Mean body weights were significantly lower for F0 pups (56%) on day 21 and F2 pups of days 1 (8%), 7 (13%) and 21 (21%). Physical development landmarks (pinna unfolding, incisor eruption, and eye opening) were delayed at the high-dose level, but were considered to be secondary to the decreased body weight. In the F0 generation, F1 litters, the mean number of live pups/litter was significantly deceased at the mid- and high-dose levels (11.0 and 10.3, respectively) on day 0, compared to the control value (12.3); on day 4 (precull), the number of live pups/litter was decreased at the high-dose level (9.1), compared to the control (11.8). Because the number of live pups/litter in treated animals in the F1 generation, F2 litters, were comparable to control values, the observed differences in the F1 litters were not considered to be treatment-related. The gestation length was significantly shorter in the high-dose, F1 litters (21.7 days *vs* 22.1 days for control), the value was within the historical control range.

Based on the results of the study (liver weight increases and histopathological lesions in liver and kidney), the LOAEL for systemic toxicity was established at 30 ppm (2.1 mg/kg/day, males; 2.5 mg/kg/day, females), the NOAEL was established at 10 ppm (0.7 mg/kg/day, males; 0.9 mg/kg/day, females).

Based on the results of this study (reduced fetal body weights and delayed physical development), the LOAEL for reproductive toxicity was established at 100 ppm (7.3 mg/kg/day, males; 8.4 mg/kg/day, females), the NOAEL was established at 30 ppm (2.1 mg/kg/day, males; 2.5 mg/kg/day, females).

This study is acceptable-guideline, and satisfies requirements [870.3700, §83-4] for a reproductive toxicity study in the rat.

4.5 Chronic Toxicity

Adequacy of data base for chronic toxicity: The data base for chronic toxicity is considered complete. No additional studies are required at this time.

Acceptable chronic toxicity studies in the rat and dog and oncogenicity studies in the rat and mouse were reviewed. In the feeding studies in rodents and dogs, the liver was again identified as the target organ for toxicity. Findings similar to the subchronic studies included increased liver weights in treated animals all of these studies and histological examination revealed an increased incidence hepatic lesions. The carcinogenicity studies in the rat and mouse showed increased

incidence of adenomas and carcinomas; neoplastic lesions were not observed in the dog study.

4.5.1 OPPTS 870.4100a Chronic Feeding – Rat

Executive Summary: In a chronic toxicity/oncogenicity study (43927302), diclofop-methyl was administered to a total of 80 Wistar rats/sex/dose in the diet at dose levels of 0, 4.5, 45, or 450 ppm (0, 0.23, 2.3, or 25 mg/kg body weight/day for males, and 0, 0.3, 3, or 32 mg/kg/day for females) for up to 2 years. Ten rats/sex/dose were sacrificed after 12 months. Twenty rats/sex/dose were treated in a 24-month toxicity study and 50 rats/sex/dose comprised a 24-month carcinogenicity study. Fifty additional female rats were administered the compound at 900 ppm (79 mg/kg body weight/day) for 24 weeks.

Chronic Toxicity (Carcinogenicity Summarized below): Dose levels up to 450 ppm did not increase mortality over controls. The 900 ppm dose was not tolerated by the females tested and this dose group was terminated after 24 weeks. At 45 ppm, males and females in the 24-month studies showed signs of liver toxicity, including increased liver weights, impaired lipid and protein metabolism, and increased liver enzyme activity. Related microscopic findings were hepatocellular hypertrophy, epithelial lipofuscin storage, and necrosis; the effects were more pronounced in males. Liver cell enlargement was observed in both sexes at 45 ppm in the 12-month study. Spleen weight was decreased at 450 ppm. Increases in kidney weight in males were significant and dose-related at 45 ppm. Also at 45 ppm, kidneys of both sexes exhibited a shift in lipofuscin storage from focal to diffuse. At the high dose of 450 ppm, body weight gain was significantly reduced in both sexes in the 12-month and two 24-month studies. In the 24-month studies, treatment-related increases in absolute and/or relative liver and kidney weights were observed at the high dose in males and females. The high dose caused significant decreases in red blood cell parameters, impaired lipid and protein metabolism, and increased liver enzyme activity, more so in males than in females. In addition to the microscopic liver abnormalities seen from the 45 ppm dose, the high dose produced a significant showing of atypical eosinophilic foci and basophilic foci in both sexes.

The LOAEL for systemic toxicity is 45 ppm in male (2.32 mg/kg/day) and female (3.05 mg/kg/day) rats, based on liver toxicity manifested as increased organ weight, impaired lipid and protein metabolism, increased enzyme activity, hepatocellular hypertrophy, and increased epithelial lipofuscin storage, and increased kidney weight and a shift from focal to diffuse lipofuscin storage pattern. The NOAEL is 4.5 ppm in males (0.23-0.27 mg/kg/day) and females (0.3 mg/kg/day). The low dose of 4.5 ppm was adequate to establish a NOAEL.

The high dose of 450 ppm was adequate to assess the chronic toxicity and carcinogenic potential of diclofop-methyl in male and female rats.

The study is acceptable (guideline) and fulfills the requirement for chronic toxicity study (83-1, 870.4100) the rat.

4.5.2 OPPTS 870.4100a Chronic Feeding – Rat

Executive Summary: In this combine chronic toxicity/oncogenicity study (92036057), rats were fed diets containing diclofop-methyl at concentrations of 0, 2.0, 6.3, or 20 ppm (0, 0.1, 0.32,

0.99 mg/kg/day, males; 0, 0.12, 0.39, 1.25 mg/kg/day, females) for 24 months.

Chronic Toxicity: No treatment-related clinical effects were observed during the study. After 24 months of treatment, mortality of low- and mid-dose males and all treated female groups were comparable to control values; mortality of high-dose males was less than the control value. Body weights all male treatment groups and low- and mid-dose females were comparable to control values; for high-dose females body weights were slightly decreased (4 to 9%) from week 26 through 78. The decrease observed in high-dose females was not considered toxicologically significant and not sufficient to establish this finding as an MTD.

Clinical pathology results showed effects in hematology and clinical chemistry; urinalysis values were not affected by treatment. Decreases in hemoglobin concentration in mid- and high-dose males at weeks 28 and 53, respectively; hemoglobin concentrations at 79 and 104 seeks were comparable to control values. Females showed sporadic changes in hemoglobin concentrations through week 79; at week 104, decreases were noted in all of the treated female groups. Consistent clinical chemistry effects were observed at 20 ppm, and included decreased cholesterol and total lipids and increased ALT (SGPT).

At terminal sacrifice, increased organ weights and increased incidence of non-neoplastic findings were observed. For females increases in relative heart, liver, and kidney weights were observed at 6.3 ppm, and relative thyroid, adrenals and liver weights at 20 ppm. Organ weights of low-dose females and all treated male groups were unaffected by treatment. Non-neoplastic lesions were observed in mid- and high-dose males, where increased incidence of foam cell aggregation (34% and 49%, respective to dose) and cholesterol clefts (7.1% and 13%, respective to dose) were observed in the lungs. These lesions in the lung may be an age-related finding and not a treatment-related effect of diclofop-methyl. High-dose males showed an increased incidence (7.3%) of craniopharyngeal cysts in the pituitary, while high-dose females showed increased incidence of uterine lesions (cystic endometrial hyperplasia, 11.6% and endometrial polyps, 16.2%).

Although neoplastic lesions were observed in this study, the oncogenicity portion of this study was found to be unacceptable (MTD not achieved). The full oncogenic potential of diclofop-methyl could not the assessed in this study.

The LOAEL for chronic toxicity was established at 6.3 ppm (0.32 mg/kg/day), based on increased relative organ weights (heart, liver, kidneys) in females and increased incidence of histopathological lesions (foam cell aggregation and cholesterol clefts in lungs) in males. The NOAEL was established at 2 ppm (0.1 mg/kg/day).

The study is acceptable (guideline) and fulfills the requirement for chronic toxicity study (83-1, 870.4100) the rat.

4.5.3 OPPTS 870.4100b Chronic Oral Toxicity - Dog

Executive Summary: In this chronic oral toxicity study (92036058, reformat of 00071870), Beagle dogs 6/sex/dose) were fed diets containing diclofop-methyl at concentrations of 0 (basal

diet), 8, 25, or 80 ppm (0.20, 0.63, 2.0 mg/kg/day).

All dogs survived to terminal sacrifice. After one year of treatment, one high-dose female showed marked deterioration in health status, which was attributed to treatment. All other animals were free of clinical signs of toxicity.

The affected female showed loss of body weight and changes in hematology (decreased hemoglobin concentration, increased leukocytes and increased thrombocytes) and clinical chemistry (increased AST, ALT, ALP) parameters.

Excluding the affected high-dose female, body weights of remaining animals were not affected by treatment. Food consumption of treated animals was comparable to control values.

At study termination pathological changes were observed in females; treated males did not show any treatment-related findings. Effects in females included organ weight changes (increased absolute and relative liver weights) at the high-dose, gross findings (distinct lobular markings, bright clay-colored liver, abnormal gallbladders) in the livers of mid- and high-dose animals, and histopathological changes in mid- (fatty change) and high- (fatty change , mucous and follicles in gallbladder) animals. No treatment-related neoplastic lesions were observed in treated animals.

Based on the results of this study (gross and histopathological liver findings and increased AST, ALT, and ALP), the LOAEL was established at 25 ppm (0.63 mg/kg/day) in females; a LOAEL was not established in males. The NOAEL was established at 8 ppm (0.20 mg/kg/day) in females and 80 ppm (2.0 mg/kg/day) in males.

This study is classified as acceptable (guideline) and satisfies guideline requirements [870.4200, 83-1(b)] for a chronic toxicity study in the dog.

4.6 Carcinogenicity

Adequacy of data base for Carcinogenicity: The data base for carcinogenicity is considered complete. No additional studies are required at this time.

4.6.1 OPPTS 870.4200a Carcinogenicity Study - Rat

Executive Summary: In a chronic toxicity/oncogenicity study (43927302), diclofop-methyl was administered to a total of 80 Wistar rats/sex/dose in the diet at dose levels of 0, 4.5, 45, or 450 ppm (0, 0.23, 2.3, or 25 mg/kg body weight/day for males, and 0, 0.3, 3, or 32 mg/kg/day for females) for up to 2 years. Ten rats/sex/dose were sacrificed after 12 months. Twenty rats/sex/dose were treated in a 24-month toxicity study and 50 rats/sex/dose comprised a 24-month carcinogenicity study. Fifty additional female rats were administered the compound at 900 ppm (79 mg/kg body weight/day) for 24 weeks.

Carcinogenicity: Under conditions of this study, diclofop-methyl induced liver tumors in males and females, adrenal gland and testicular tumors in males, and uterine and thyroid tumors in females at 450 ppm (25.2 - 29.3 mg/kg/day, males; 32.4 - 36.6 mg/kg/day, females). The incidence

of combined hepatocellular adenomas and carcinomas in the two 24-month studies was 42.0% in males and 27.1% in females. Incidence of the carcinoma, detected in 26% of males and 20% of females was higher than for the adenoma, indicating malignancy. These liver neoplasms were also observed in females at 45 ppm. Analysis of the liver tumor profiles showed a significant positive trends and pairwise comparisons (control vs 450 ppm) for adenomas and/or carcinomas and combined in males and females. In addition at 450 ppm, females exhibited a significant 8% increase in incidence of thyroid follicular cell adenoma. Incidences of uterine glandular polyps (8%), testis Leydig cell tumors (26% versus 6 and 8% in concurrent and historical controls), and adrenal gland medullary adenomas (6%) in males, also showed significant trends, and were higher than the average historical controls for the performing laboratory.

A Q_1* of 7.36×10^{-2} $(mg/kg/day)^{-1}$ was calculated based on the incidence of combined liver adenomas and carcinomas in females.

This study is classified as acceptable (guideline) and satisfies the guideline requirements (870.4200, 83-2) for a carcinogenicity study in the rat.

4.6.2 OPPTS 870.4200b Carcinogenicity (Feeding) - Mouse

Executive Summary: In this oncogenicity study, HOE NMRKf mice were fed diets at 0, 2.0, 6.3, or 20 ppm (0, 0.24, 0.76, 2.5 mg/kg/day, males; 0, 0.25, 0.77, 2.6 mg/kg/day, females) diclofop-methyl for 24 months.

No clinical signs of toxicity were observed during the study. Treatment-related mortality was increased in high-dose males (64.3% *vs*. 46.1%, control). Body weight and food and water consumption of treated mice were comparable to the concurrent control values for the entire study.

Clinical pathology did not reveal any treatment-related changes in any of the hematological or urinalysis parameters; clinical chemistry findings were observed. At the high-dose level, ALP activity was significantly increased at the interim, week 88, (164% males, 455% females and terminal (139% males, 250% females) sacrifices. In 6.3 ppm males, ALP activities was elevated through week 81, but not at study termination. At the high-dose level, significant increases in ALT (SGPT) activity (63%, males, 124% females) and significant decreases in total glycerol (27% males, 60% females).

Organ weights were significantly increased at both the interim (week 88) and terminal sacrifices. At the interim sacrifice, the relative liver and kidney weights were increased in high-dose males and females; relative adrenal and brain weights were increased in high-dose females. At terminal sacrifice, the relative liver and kidney weights were increased in mid- and high-dose males and females; relative heart weights were increased in mid-dose males and high-dose males and females.

At necropsy, gross evaluations revealed swelling and discoloration in the livers, with more frequent findings in males. Histopathological examination revealed non-neoplastic lesions in the livers consisting of hepatocytic hypertrophy and eosinophilic inclusions. Auricular thrombosis of the heart was observed in high-dose males. Electronmicrographs revealed peroxisome proliferation in

the livers of high-dose animals.

For high-dose males, hepatocellular tumor rates for adenomas and carcinomas were significantly increased (trend and pairwise) by 18% (20/113) and 14% (12/85), respectively; the combined tumor rate was 28% (32/113). The tumor rate of adenomas and carcinomas of the low- and mid-dose groups were comparable to control values.

Based on the results (combined liver adenomas and carcinomas) of this study, diclofop-methyl was categorized as a likely carcinogen with a Q_1* of 2.3 x 10^{-1} $(mg/kg/day)^{-1}$.

The LOAEL for systemic toxicity was established at 6.3 ppm (0.76 mg/kg/day, males; 0.77 mg/kg/day, females) based on clinical chemistry findings (increased ALP) in males and increased relative organ weights in males (liver, kidney, heart) and females (liver, kidney), and hepatotoxicity (hypertrophy, eosinophilic inclusions, brown pigment deposits) in females. The NOAEL was established at 2 ppm (0.24, males; 0.25, females).

The study is acceptable (guideline) and fulfills the requirement for an carcinogenicity study (83-2, 870.4200) the mouse.

4.7 Mutagenicity

Adequacy of data base for Mutagenicity: The data indicate that diclofop-methyl is not mutagenic under the testing conditions and there is no mutagenic concern at the present time. The acceptable studies satisfy both the pre-1991 and new minimum initial mutagenicity testing requirements.

The data indicate that diclofop-methyl is not mutagenic under the testing conditions and there is no mutagenic concern at the present time. The acceptable studies satisfy both the pre-1991 and new minimum initial mutagenicity testing requirements.

4.7.1 Gene Mutations

4.7.1.1 Bacterial reverse mutation test in *Salmonella typhimurim*

OPPTS 870.5100
MRID 00071904 (HED 000076)
Dose range: 0 to 5000 μg/mL +/- S9
Negative for mutagenic effects
Acceptable (Guideline)

4.7.1.2 *In vitro* mammalian cell gene mutation test with Chinese hamster V79 cells

OPPTS 870.5300
MRID 41573305 (HED 008541)
Dose range: 2 to 500 μg/mL +/- S9
Test was negative up to cytotoxic doses ($\geq$ 200 μg/mL, -S9; $\geq$ 300 μg/mL, +S9).
Acceptable (Guideline)

4.7.2 Cytogenetics

4.7.2.1 *In vitro* mammalian chromosomal aberration test in primary human lymphocytes

OPPTS 870.5375
MRID 41476004 (HED 013723)
Dose range: 1 to 500 μg/mL +/- S9
Test was negative up to a cytotoxic (500 μg/mL)
Acceptable (Guideline)

4.7.2.2 *In vivo* cytogenetic test in bone marrow cells of the Chinese hamster

OPPTS 870.5385
MRID 41737901 (HED 008850)
Dose range: 0, 200, 1000, and 2000 mg/kg
Chromosomal analysis did not show any treatment-related cytogenetic aberrations up to the highest dose tested
Acceptable (Guideline)

4.7.3 Other Genotoxic Effects

4.7.3.1 Unscheduled DNA synthesis in primary rat hepatocytes *in vitro*

OPPTS 870.5550
MRID 00087816 (HED 001422)
Dose range: 0.5 to 50 μg/mL, cytotoxicity at 100 μg/mL
Did not induce significant increases in nuclear labeling of primary rat hepatocytes.
Acceptable (Guideline)

4.7.3.2 Unscheduled DNA synthesis in A549 human lung carcinoma *in vitro*

OPPTS 870.5550
MRID 41996902, 42437801 (HED 008796)
Dose range: 0.03 to 100 μg/mL ± S9
Did not induce significant increases in nuclear labeling human lung cancer cells Up to the highest dose tested.
Acceptable (Guideline)

4.8 Neurotoxicity

Adequacy of data base for Neurotoxicity: These studies are not required at this time. Review of the toxicology database did not reveal any neurotoxicity in the existing studies.

4.8.1 OPPTS 870.6100 Delayed Neurotoxicity Study - Hen

Not required

4.8.2 OPPTS 870.6200 Acute Neurotoxicity Screening Battery

Not required

4.8.3 OPPTS 870.6200 Subchronic Neurotoxicity Screening Battery

Not required

4.8.4 OPPTS 870.6300 Developmental Neurotoxicity Study

Not required

4.9 Metabolism

Adequacy of data base for metabolism: The data base for metabolism is considered to be complete. No additional studies are required at this time.

4.9.1 OPPTS 870.7485 Metabolism - Rat

Executive Summary: In this metabolism study (41573306), [dichlorophenoxy ^{14}C]-labeled Hoelon (>98%, 20.82 mCi/g) was administered to male and female Wistar rats (5/sex/group). Test compound was orally administered at a low (0.5 mg ^{14}C-Hoelon/kg), high (5 mg ^{14}C-Hoelon/kg), or repeated low dose (0.5 mg/kg/day x 14 days, followed by 0.5 mg/kg of ^{14}C-Hoelon).

The percent of the radioactivity eliminated over a 96-hour period were quantitatively similar for the low-, high-, and repeat low-dose groups; no differences were noted between sexes. Most of the radioactivity was eliminated in the feces (69.7 to 77.9%) while less was eliminated in the urine (16.4 to 18.9%); no measurable amount (< 0.01%) of radioactivity was found in expired air. Total recovery of ^{14}C-label was between 100.9 and 103.0%.

Tissue levels of radioactivity of low-dose groups were about 7 to 20 times lower than that of the high-dose groups. Within each of the three treatment groups, residual tissue radioactivity, except the ovaries (attributed to the higher fat contend), was generally similar for males and females. Residual radioactivity was found mainly in the liver, kidney and digestive tract; the highest levels of radioactivity were found in the fat.

Plasma half-life (t½) of residual radioactivity was similar for low- and high-dose groups, with no differences due to sex (15 hr, males; 14 hr, females). Pharmacokinetic evaluation of the area under the curve (AUC) of high-dose groups (581 to 606 μg x hr/g of plasma) was approximately 10 times higher than that of the low-dose groups (47.0 to 57.5 μg x hr/g of plasma). Peak plasma levels were reached after 4 hr in both the low- (2.05 μg/g of plasma, males; 2.32 μg/g of plasma, females) and high- (21.0 μg/g of plasma , males; 22.1 μg/g of plasma , females) dose groups.

The metabolic profiles showed up to eight urinary and six fecal metabolites; no parent compound was identified in either the urine or feces. Two metabolites were identified in both the urine (U) and feces (F): U7, F4 = hydroxylated parent compound [2-(4-(2',4'-dichloro-5-hydroxyphenoxy)phenoxy)propionic acid] and U2, F3 = sulfate conjugate of U7, F4; a third urinary metabolite, U8, was identified as deesterified parent compound [2-(4-(2',4'-

dichlorophenoxy)phenoxy) propionic acid]. As percents of the administered doses, U2 = 10.2 to 13.9% in males and 3.2 to 5.4% in females, U7 = 2.3 to 2.8% in males and 1.6 to 1.9% in females, and U8 = 0.4 to 2.5% in males and 2.9 to 8.3% in females. For the fecal metabolites, F3 = 17.3 to 30.5% in males and 32.2 to 45.7% in females and F4 = 9.4 to 15.4% in males and 3.7 to 6.2% in females. An unidentified fecal metabolite accounted for 8.2 to 9.1% of the administered dose in males and 4.9 to 6.6%, in females other unknown minor metabolites accounted for 1.6 to 3.3% of the dose in males and 2.1 to 6.4%, in females.

The study is acceptable (guideline) and fulfills the requirement for a metabolism study (85-1, 870.7485) the rat.

5.0 HAZARD ENDPOINT SELECTION

5.1 Summary of Toxicological Dose and Endpoints

The doses and toxicological endpoints selected and Margins of Exposures for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary (Females 13 - 50)	NOAEL = 10 mg/kg/day	Decreased fetal body wts, distended ureters, skeletal abnormalities. These effects could be attributed to a single dose.	870.3700 Developmental toxicity study in the rat
	UF = 100	Acute RfD = 0.1 mg/kg/day	
Acute Dietary (General Population including Infants and Children)	None	No endpoint selected	None
Chronic Dietary (Non-cancer)	NOAEL = 0.23 mg/kg/day	Based on increased relative liver and kidney wts, liver enzymes, liver histopathology (hypertrophy, lipofuscin storage). Effects and NOAEL consistent with other studies in mouse and dog.	870.4300 Chronic toxicity study in the rat
	UF = 100	Chronic RfD = 0.0023 mg/kg/day	
Short-Term (Dermal)	NOAEL = 5 mg/kg/day	Based on increased liver enzymes, proteins, and absolute and relative liver weights.	870.3200 21-Day Dermal Toxicity Study in the Rat
Intermediate Term (Dermal)	NOAEL = 5 mg/kg/day	Based on increased liver enzymes, proteins, and absolute and relative liver weights.	870.3200 21-Day Dermal Toxicity Study in the Rat

Long-term Non-cancer (Dermal)	Based on the use pattern (applied at the rate of 454 g ai/acre up to a maximum of 1 application/crop cycle), this risk assessment is not required		
Inhalation (Short and Intermediate)	Oral NOAEL = 0.23 mg/kg/day	Appropriate route-to-route extrapolation should be performed for these risk assessments. Inhalation exposure values should be converted to equivalent oral doses and compared to the oral NOAEL.	
Cancer (Dermal and Inhalation)	Q_1* of 2.3 x 10^{-1} $(mg/kg/day)^{-1}$	Based on liver adenomas and carcinomas with significant trend and pair-wise comparisons.	870.4200 Mouse Carcinogenicity Study

5.2 Dermal Absorption

Dermal Absorption Factor: 15%. The dermal absorption factor was not used since an acceptable dermal toxicity study was available.

5.3 Classification of Carcinogenic Potential

Diclofop-methyl is classified as a **LIKELY** human carcinogen with a **Q_1***.

For the purpose of risk characterization, a low-dose extrapolation model be applied to the experimental animal tumor data in the mouse. A **Q_1* of 2.3 x 10^{-1} $(mg/kg/day)^{-1}$** should be used for human risk assessment.

6.0 FQPA CONSIDERATIONS

6.1 Special Sensitivity to Infants and Children

The data provided no indication of increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure to diclofop-methyl. In the prenatal developmental toxicity studies in rats and rabbits on the diclofop-methyl, no effects in the offspring were observed at maternally toxic doses.

6.2 Recommendation for a Developmental Neurotoxicity Study

Neither the subchronic or chronic toxicity studies in mice, rats and dogs, the developmental toxicity studies in rats and rabbits, or the reproduction study in rats indicated that the nervous system was specifically affected by treatment with diclofop-methyl. Thus, there is no indication that diclofop-methyl is a neurotoxic herbicide.

There are no acute (§81-8, 870.6200a) and subchronic (§82-7, 870.6200b) neurotoxicity studies available (not required).

6.3 FQPA Safety Factor Committee Recommendation

FQPA Safety Factor met on April 10, 2000 and concluded that the data do not support retention of an FQPA safety factor and recommended that it be reduced to 1X (factor removed).

7.0 OTHER ISSUES

On March 27, 2000, a joint meeting of the Health Effects Division's Mechanism of Toxicity Assessment Review Committee and Cancer Peer Review Committee met to discuss mode of action on liver carcinogenicity of diclofop-methyl. The mechanism of action of diclofop-methyl were evaluated using the criteria discussed in the ISLI workshop to support characterization of a nongenotoxic hepatocarcinogenic substance as peroxisome proliferator. Although the committee agreed that there is evidence of peroxisome proliferation, based on the ILSI criteria, the submitted studies lack the depth and quality to unequivocally establish as a peroxisome proliferation. The studies submitted were dated and do not take advantage of more recent methodology (e.g. measurement of more sensitive hepatic enzymes, morphometric analysis of peroxisomes). Further, there was no direct measurement of cell proliferation; the committee felt that time-dose effects on DNA synthesis would establish the sequence of events associated with peroxisome proliferation.

On February 10, 1993 the carcinogenic potential of diclofop-methyl was reviewed by the CARC . At this meeting, a combined chronic feeding/carcinogenicity study in the rat and a carcinogenicity study in the mouse were evaluated. The mouse study was found to be acceptable, while the rat study was not (MTD not achieved). The CARC classified diclofop-methyl as Group C (possible human carcinogen) and recommended a linear low-dose extrapolation approach for the quantification of human cancer risk. A Q_1* of 2.3×10^{-1} $(mg/kg/day)^{-1}$ was determined from the mouse carcinogenicity study.

On January 5, 2000, the CARC met again to discuss the newly submitted rat study and reclassify diclofop-methyl under the Agency's Draft Guidelines for Carcinogen Risk Assessment [1996, 1999]. Data included an acceptable rat chronic/carcinogenicity study, a revised statistical analysis of the rat tumor data as well as data on structurally-related compounds. The CARC reclassified diclofop-methyl as **"likely to be carcinogenic to humans"**. The Q_1* from the mouse carcinogenicity study was again selected for risk assessment.

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9.0 APPENDICES

9.1 Toxicity Profile Summary Tables

9.1.1 Acute Toxicity Table

Acute Toxicity Data on Diclofop-methyl

OPPTS Guideline No.	Study Type	MRID Nos	Results	Toxicity Category
870.1100	Acute Oral	41476001 92036052	Male: 481 mg/kg Female: 500-630 (estimate) mg/kg Combined 512 (428-636) mg/kg	II
		00123982	Male: 580 mg/kg	II
		00123983	Female: 557 mg/kg	II
870.1200	Acute Dermal	00071522 92036013	Male: 580 mg/kg	II
		00032595	Female: 557 mg/kg	
870.1300	Acute Inhalation	00032595	Male and female > 3.83 mg/L	IV
		41573304	Male and female > 4.75 mg/L	IV
		00032595	Male and female > 3.83 mg/L	IV
870.2400	Primary Eye Irritation	42428601	Slight ocular irritant, Conjunctival redness and discharge at 24 hr, cleared by 72hr	III
870.2500	Primary Skin Irritation	40213506	Slight irritant, PII = 0.8 (0 to 72 hr)	IV
870.2600	Dermal Sensitization	41476003 92036047	Buehler: Negative	NA
		41476002 41476003 92036046	Maximization: Moderate to severe sensitizer	NA

9.1.2 Subchronic, Chronic and Other Toxicity Table

Toxicity Profile for Diclofop-Methyl (110902, 319A)

Study Type	NOAEL	LOAEL
82-1(a): 90-Day Feeding - Rat MRID No.: 42573301 / 02 HED Doc No.: 010435 (20 Jul 93) Acceptable (Guideline)	NOAEL (M/F): 1.6 / 1.8	LOAEL (M/F): 6.3 / 7.1 Clinical chem, perox proliferation, liver hypertrophy
82-1(a): 90-Day Feeding - Mouse MRID No.: 42593901 HED Doc No.: 010435 (9 Jul 93) Acceptable	NOAEL (M/F): Not established	LOAEL (M/F): 0.3 / 0.4 Clinical chem, perox proliferation, liver necrosis
82-2: 21-Day Dermal - Rat MRID No.: 92036048 , 41476004 HED Doc No.: 013723 Acceptable	Syst NOAEL: 5 Dermal NOAEL ≥125 mg/kg/day	Syst LOAEL: 25 Based on increased liver enzymes, proteins, and absolute and relative liver weights Dermal LOAEL > 125 mg/kg/day
83-1/2: Chronic Feeding/ Carcinogenicity - Rats MRID: 43927302 HED Doc: 013313 Acceptable	Syst NOAEL (M/F): 0.23 / 0.3 Cancer NOAEL (M/F):2.3 / 3.0	Syst LOAEL (M/F): 2.32 /3.05 Increased liver and kidney weights, hepatocellular hypertorphy, histopathology (lipofusin storage) Cancer LOAEL (M/F): 25 / 32 Increased hepatocelular adenomas and carcinomas. Thyroid follicular cell adenoma
83-1/2: Chronic Feeding/ Carcinogenicity - Rats MRID: 92036057 (Reformat of 00070615) HED Doc: 008541 (1 Jul 91) 83-1 Acceptable (guideline) 83-2 Unacceptable (guideline)	Syst NOAEL (M/F): 1.6 Cancer NOAEL (M/F) Not achieved	Syst LOAEL (M/F): 19 Increased relative liver, heart and kidney weights. Cancer LOAEL (M/F): 1.6 MTD not achieved
83-1: 15-Month Feeding - Dog MRID: 92036039 (reformat of 00071913) HED Doc No.: 008541 (21 Feb 91) Acceptable (guideline)	NOAEL (M/F): 2.0 / 0.2	LOAEL (M/F): not established / 0.63 Clinical chem, perox proliferation, liver histopathology
83-2: Carcinogenicity - Mice MRID: 92036058 (Reformat of 00071870) HED DOC : 008541 (19 Mar 91)	NOAEL (M/F): 0.24 / 0.25	LOAEL (M/F): 0.76 / 0.77 Clinical chem, perox proliferation, liver hypertrophy

Study Type	NOAEL	LOAEL
83-3(a): Developmental Tox - Rat MRID No.: 92036042 (Reformat of 00071908) HED Doc: 008541, 010486 (Hist control)	Maternal NOAEL: not established Devel NOAEL 10	Syst LOAEL: 10 mg/kg/day Increased liver weights Devel LOAEL: 32 Decreased fetaal body wt and crown-rump length
83-3(b): Developmental Tox - Rabbit MRID No.: 92036043 (Phase III reformat of 00139613) HED Doc: 004312	Maternal NOAEL = 0.30 mg/kg/day Devel NOAEL ≥ 3.0 mg/kg/day	Maternal LOAEL = 3.0 mg/kg/day, Based on significantly increased absolute liver and kidney weights, decreased body weight gain, and reduced food consumption. No treatment-related developmental effects were noted at any dose level. The developmental LOAEL was not established.
83-4: 2-Generation Reproduction - Rat MRID: 42543101, 42060501 HED Doc: 011072 (13 Jun 94)	Syst NOAEL = 10 ppm (0.7 mg/kg/day, males 0.9 mg/kg/day, females)the Repro NOAEL = 30 ppm (2.1 mg/kg/day, males 2.5 mg/kg/day, females)	Syst LOAEL = 30 ppm (2.1 mg/kg/day, males; 2.5 mg/kg/day, females) Based on the results of the study (liver weight increases and histopathological lesions in liver and kidney) Reprod LOAEL = 100 ppm (7.3 mg/kg/day, males; 8.4 mg/kg/day, females Based on the results of this study (reduced fetal body weights and delayed physical development), the),
870.5100: Bacterial reverse mutation test in Salmonella typhimurim MRID: 00071904 HED Doc: 000076	Dose range: 0 to 5000 μg/mL +/- S9 Negative for mutagenic effects Acceptable (Guideline)	
870.5300: In vitro mammalian cell gene mutation test with Chinese hamster V79 cells MRID: 41573305 HED Doc: 008541	Dose range: 2 to 500 μg/mL +/- S9 Test was negative up to cytotoxic doses (≥ 200 μg/mL, -S9; ≥ 300 μg/mL, +S9). Acceptable (Guideline)	
870.5375: In vitro mammalian chromosomalaberration test in primary human lymphocytes MRID 41476004 HED 013723	Dose range: 1 to 500 μg/mL +/- S9 Test was negative over the dose range +S9) Acceptable (Guideline)	
870.5385: In vitro cytogenetic test in bone marrow cells of the Chinese hamster MRID 41737901 HED 008850	Dose range: 0, 200, 1000, and 2000 mg/kg Chromosomal analysis did not show any treatment-related cytogenetic aberrations Acceptable (Guideline)	
870.5550: UDS Assay in primary rat hepatocytes in vitro MRID: 00087816 HED Doc: 001422	Dose range: 0.5 to 50 μg/mL, cytotoxicity at 100 μg/mL Did not induce significant increases in nuclear labeling of primary rat hepatocytes. Acceptable (Guideline)	
870.5550: Unscheduled DNA synthesis in A549 human lung carcinoma in vitro MRID: 41996902, 42437801 HED Doc: 008796	Dose range: 0.03 to 100 μg/mL ± S9 Did not induce significant increases in nuclear labeling human lung cancer cells. Acceptable (Guideline)	

Study Type	NOAEL	LOAEL
: Mutagenicity -Other genotoxic effects MRID: 00087820 HED Doc: 001422	Dose range: 250, 500, 1000 μg/mL ± S9 Mitotic gene conversions not increaed in yeast strain over spontaneous rate ± S9 Acceptable (Guideline)	
85-1: Metabolism - Rat MRID No.: 41573306 HED Doc No.: 008541	Acceptable	
85-2: Dermal Absorption w/ 3EW & 3EC - Rat MRID No.: 42364601 HED Doc No.: 010334 (21 Sep 92)	Dermal absorption factor = 15% at 10 hours	

9.2 Summary of Toxicological Dose and Endpoints for Diclofop-methyl for Use in Human Risk Assessment

The doses and toxicological endpoints selected and Margins of Exposures for various exposure scenarios are summarized below.

9.2 Summary of Toxicological Dose and Endpoints for Diclofop-methyl for Use in Human Risk Assessment

Exposure Scenario	Dose Used in Risk Assessment UF and FQPA SF [a]	Endpoint for Risk Assessment [b]	Study and Toxicological Effects
Acute Dietary (Females 13 - 50)	NOAEL = 10 mg/kg/day UF = 100 Acute RfD = 0.1 mg/kg/day FQPA SF = 1	$\mathbf{aPAD} = \frac{\mathbf{Acute\ RfD}}{\mathbf{FQPA\ SF}}$ = 0.1 mg/kg/day	870.3700 Developmental toxicity study in the rat LOAEL = based on decreased fetal body weights, distended ureters, skeletal abnormalities. These effects could be attributed to a single dose.
Acute Dietary (General Population including Infants and Children)	None	No endpoint selected	None
Chronic Dietary (Non-cancer)	NOAEL = 0.23 mg/kg/day UF = 100 Chronic RfD = 0.1 mg/kg/day FQPA SF = 1	$\mathbf{cPAD} = \frac{\mathbf{Chronic\ RfD}}{\mathbf{FQPA\ SF}}$ = 0.0023 mg/kg/day	870.4300 Chronic toxicity study in the rat LOAEL = based on increased relative liver and kidney weights, liver enzymes, liver histopathology (hypertrophy, lipofuscin storage). Effects and NOAEL consistent with other studies in mouse and dog.
Short-Term (Dermal)	NOAEL = 5 mg/kg/day	Acceptable MOE = 100	870.3200 21-Day Dermal Toxicity Study in the Rat LOAEL = based on increased liver enzymes, proteins, and absolute and relative liver weights
Intermediate Term (Dermal)	NOAEL = 5 mg/kg/day	Acceptable MOE = 100	870.3200 21-Day Dermal Toxicity Study in the Rat LOAEL = based on increased liver enzymes, proteins, and absolute and relative liver weights.
Long-term Non-cancer (Dermal)	Based on the use pattern (applied at the rate of 454 g ai/acre up to a maximum of 1 application/crop cycle), this risk assessment is not required		
Inhalation (Short and Intermediate)	Oral NOAEL = 0.23 mg/kg/day	Appropriate route-to-route extrapolation should be performed for these risk assessments. Inhalation exposure values should be converted to equivalent oral doses and compared to the oral NOAEL.	
Cancer (Dermal and Inhalation)	Q_1^* of 2.3×10^{-1} $(mg/kg/day)^{-1}$	870.4200 Mouse Carcinogenicity Study Q_1^* based on liver adenomas and carcinomas with significant trend and pair-wise comparisons in female mice	

[a] FQPA SF = FQPA Safety Factor

[b] PAD = Population Adjusted Dose for acute (a) and chronic (c) exposure scenarios.